The prevalence of cancer associated systemic inflammation: Implications of T prognostic studies using the Glasgow Prognostic Score

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ARTICLE INFO

Keywords:
Cancer
TNM stage
Systemic Inflammation
Glasgow Prognostic Score
modified Glasgow Prognostic Score

ABSTRACT

The prognostic importance of SIR in patients with cancer is widely recognised. More recently it has become clear that the systemic inflammatory response is an important etiologic factor in the development of cancer cachexia. Two recent meta-analysis carried out in 2017 and 2018 were interrogated and the number of patients with specific cancer types were identified. The percentage of patients with operable cancer (n > 28,000) who were systemically inflamed varied from 21% to 38%. The percentage of patients with inoperable cancer (n > 12,000) who were systemically inflamed varied from 29% to 79%. Overall, the percentage of patients (n > 40,000) who were systemically inflamed varied from 28% to 63% according to tumour type. The most commonly studied cancer was colorectal cancer (n~10,000 patients) and 40% were systemically inflamed.

1. Introduction

Cancer is the second leading cause of death globally being re-sponsible for 9.6 million deaths in 2018 (World Health Organization, 2018. In westernised countries, it has been estimated that one in three people will develop cancer in their lifetime, and one in four will die from it (Bosanquet and Sikora, 2004, World Health Organization, 2017). A curative intent will always be the aim of any surgical or on-cological treatment however many patients will go on to develop dis-seminated disease requiring best supportive care (Dolan et al., 2017b, Dolan et al., 2017a).

In 2014 McAllister and Weinberg concluded that tumour related systemic inflammation was the “seventh hallmark of cancer” and the “tip of the iceberg” in terms of cancer biology and treatment (McAllister and Weinberg, 2014, Mantovani et al., 2008, Paulsen et al., 2017). Furthermore, in two recent meta-analyses Dolan and co-workers showed that widely used clinical markers of the systemic inflammatory response (SIR) (C-reactive Protein [CRP], albumin, neutrophils and platelets) had prognostic value in patients with operable and in ad-vanced cancer (Dolan et al., 2017a, Dolan et al., 2017b). Indeed, the activation of the systemic inflammatory response has been strongly implicated in the aggressiveness of the disease and development of cachexia with associated deleterious outcomes. It has become clear that the systemic inflammatory response is an important etiologic factor in the development of cancer cachexia (Arends et al., 2017, Cederholm et al., 2017, Cederholm et al., 2019). Therefore, it is of considerable importance to understand the prevalence of the systemic inflammatory response in patients with primary operable cancer and advanced op-erable cancer in order to develop strategies to mitigate the effects of the systemic inflammatory response, especially in tumour types where the prevalence is high.

The prognostic application of markers of the SIR in patients with cancer are usually based around composite ratios or scores of different circulating white blood cells or acute phase proteins; representing the systemic responses of two different organs, lymphoid/myeloid tissue and liver respectively (Dolan et al., 2018b). The most widely validated example of a composite ratio would be the neutrophil lymphocyte ratio (NLR) based on the ratio of circulating neutrophil and lymphocyte counts (Dolan et al., 2017b). While it is clear that composite ratios such as the NLR have prognostic value, there is a large variation in the specific threshold levels used which makes comparison of studies dif-ficult (Dolan et al., 2017a, Dolan et al., 2017b, Guthrie et al., 2013a, Watt et al., 2015). The most widely validated example of a cumulative scores is the Glasgow Prognostic Score (GPS) and the modified Glasgow Prognostic Score (mGPS) based on the acute phase proteins C-reactive protein and albumin. The advantage of cumulative scores is that they are based on validated laboratory reference ranges and the advantage of the GPS/mGPS is that consistent thresholds that allow for direct comparison of the SIR across different institutions and geographical locations (Dolan et al., 2017b, Dolan et al., 2017a).

While the prognostic importance of the SIR in patients with both operable and inoperable cancers is widely recognised, the level of

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systemic inflammation in patients with cancer across the literature has not been formally assessed. Therefore, the aim of the present study was to determine the prevalence of systemic inflammation as measured by the GPS/ mGPS in patients with either operable or inoperable cancer.

2. Methods

The present review of published literature was based on that of two previous systematic reviews (Dolan et al., 2017b, Dolan et al., 2017a) undertaken according to a pre-defined protocol described in the PRISMA-P statement. These reviews recently reported on both operable cancer and advanced inoperable cancer. Briefly, these systematic re-views (Dolan et al., 2017b, Dolan et al., 2017a) carried out a wide-ranging literature search to identify studies conducted from January 1947 to 31 st January 2018. Medical subject heading (MeSH) terms (Cancer, GPS, Glasgow Prognostic Score, mGPS and modified Glasgow Prognostic Score), were used in the US National Library of Medicine (MEDLINE), the Excerpta Medica database (EMBASE) and the Cochrane Database of Systematic Reviews (CDSR) to identify published papers and abstracts.

Animal studies, those not in cancer patients, and trials not available in English were excluded. Where there were multiple publications from the same cohort the most recent paper was included. Once further ex-clusions outlined below were carried out, the bibliographies of all in-cluded articles were subsequently hand searched to identify any addi-tional studies. Only studies that had greater than 100 observations and reported survival were considered in the final analysis.

3. Statistics

Studies were reviewed and the number of patients with breast, bladder, gynaecological, prostate, gastrointestinal, haematological, renal, colorectal, head and neck, hepato, pancreato, biliary, pulmonary and multiple types of cancer types were grouped into tables for oper-able, inoperable and combined studies. The individual number of pa-tients with elevated CRP and albumin readings were also included. No meta analysis was carried out since it could be considered as a narrative review of previous systematic reviews(Dolan et al., 2017b, Dolan et al., 2017a).

4. Results

4.1. Study selection process

The review of existing systematic reviews(Dolan et al., 2017b, Dolan et al., 2017a) led to a review of the full text of 104 articles. A further 36 articles were identified from bibliographies and were in-cluded in this narrative review leading to a final total of 140 articles. The details of the 140 studies included in the review are shown in Table 1.

4.2. Studies of the GPS/ mGPS in patients with breast cancer

No articles were identified in patients with operable breast cancer (Table 1). Two studies including 181 patients were identified in in-operable breast cancer. These studies included both retrospective (n = 1) and prospective studies (n = 1). These included studies carried out in the UK (n = 1) and Germany (n = 1). In total 81 (45%) of patients were systematically inflamed (Tables 1 and 2).

4.3. Studies of the GPS/ mGPS in patients with bladder cancer

Two studies including 2133 patients were identified in operable bladder cancer. These studies were both retrospective studies (n = 2). These included studies carried out in Italy (n = 1) and Japan (n = 1). In total 723 (34%) of patients were systematically inflamed (Tables 1 and 2). A single study was identified in patients with inoperable bladder cancer. This contained 67 patients, was prospective, carried out in Korea and showed that 34 (51%) of patients were systemically in-flamed.

4.4. Studies of the GPS/ mGPS in patients with gynaecological cancer

Three studies including 724 patients were identified in operable gynaecological cancer. These studies included both retrospective (n = 2) and prospective studies (n = 1). These included studies carried out in Austria (n = 1), Japan (n = 1) and China (n = 1). In total 186 (26%) of patients were systematically inflamed (Tables 1 and 2).

Three studies including 870 patients were identified in inoperable gynaecological cancer. These studies included both retrospective (n = 2) and prospective studies (n = 1). These included studies carried out in multiple countries (n = 1), Austria (n = 1) and China (n = 1). In total 309 (36%) of patients were systematically inflamed (Tables 1 and 2).

4.5. Studies of the GPS/ mGPS in patients with prostate cancer

No articles were identified in patients with operable prostate cancer (Tables 1 and 2). Two studies including 223 patients were identified in inoperable prostate cancer. These studies included both retrospective (n = 1) and prospective studies (n = 1). These included studies carried out in multiple countries (n = 1) and Japan (n = 1). In total 65 (29%) of patients were systematically inflamed (Tables 1 and 2).

4.6. Studies of the GPS/ mGPS in patients with gastro-oesophageal cancer

Twenty-five studies including 7,693 patients were identified in op-erable gastro-oesophageal cancer. These studies included both retro-spective (n = 24) and prospective studies (n = 1). These included studies carried out in Japan (n = 13), UK (n = 5), China (n = 3), Germany (n = 2), Ireland (n = 1) and Italy (n = 1). In total 1,617 (21%) of patients were systematically inflamed (Tables 1 and 2).

Eleven studies including 1,897 patients were identified in inoper-able gastro-oesophageal cancer. These studies included both retro-spective (n = 10) and prospective studies (n = 1). These included studies carried out in the UK (n = 3), Japan (n = 3), Korea (n = 2), China (n = 1), Czech Rep (n = 1) and Taiwan (n = 1). In total 1032 (54%) of patients were systematically inflamed (Tables 1 and 3).

4.7. Studies of the GPS/ mGPS in patients with haematological cancer

Two studies including 430 patients were identified in inoperable haematological cancer. All studies were retrospective. These included studies carried out in China (n = 1) and Korea (n = 1). In total 340 (79%) of patients were systematically inflamed (Tables 1 and 3).

4.8. Studies of the GPS/ mGPS in patients with renal cancer

Seven studies including 2417 patients were identified in operable renal cancer. These studies included both retrospective (n = 6) and prospective studies (n = 1). These included studies carried out in the UK (n = 2), Japan (n = 4) and Korea (n = 1). In total 717 (30%) of patients were systematically inflamed (Tables 1 and 2).

Two studies including 142 patients were identified in inoperable renal cancer. These studies included both retrospective (n = 1) and prospective studies (n = 1). These studies were both carried out in the UK. In total 101 (45%) of patients were systematically inflamed (Tables 1 and 3).

4.9. Studies of the GPS/ mGPS in patients with colorectal cancer

Twenty-nine studies including 8,832 patients were identified in

Table 1
Studies using mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
Breast cancer Operable												
1.					–				–	–	–	
Breast cancer Inoperable												
1.	Al Murri et al., 2006	Retrospective	Breast cancer	UK	96	GPS (0/1/2)	45 (47)	6 (6)	51 (53)	39 (41)	6 (6)	Chemotherapy and endocrine therapy
2.	Honecker et al., 2018	Prospective	Breast cancer	Germany	85	GPS (0/1/2)	36	17	49 (57.6)	22 (25.9)	14 (16.5)	First line chemotherapy
Combined Total					181				100 (55.2)	61 (33.7)	20 (11.1)	
Bladder cancer Operable												
1	Ferro et al., 2015	Retrospective	Bladder cancer	Italy	1037	mGPS (0/1/2)	391 (37.7)	97 (9.4)	646 (62.3)	297 (28.6)	94 (9.1)	77.1% received adjuvant chemotherapy
2	Kimura et al., 2019	Retrospective	Bladder cancer	Japan	1096	mGPS	_	_	764 (69.7)	299 (27.3)	33 (3.0)	4.0% patients received adjuvant chemotherapy
Bladder cancer Inoperable												
1.	Hwang et al., 2012	Prospective	Bladder cancer	Korea	67	GPS (1&2)	30 (44.8)	21 (31.3)	33 (49.3)	17 (25.4)	17 (25.4)	Treated with chemotherapy
Combined Total					2200				1443 (65.6)	613 (27.9)	144 (6.5)	
Gynaecological cancer Operable												
1.	Hefler-Frischmuth et al., 2010	Prospective	Vulval cancer	Austria	93	GPS (0/1/2)	_	_	72 (77.4)	16 (17.2)	5 (5.4)	Adjuvant treatment not specified
2.	Saijo et al., 2017	Retrospective	Endometrial cancer	Japan	431		51 (11.8)	21 (4.9)	376 (87.2)	38 (8.8)	17 (4.0)	Adjuvant chemotherapy in high risk patients
3.	Liu et al., 2017	Retrospective	Ovarian cancer	China	200	mGPS (0/1/2)	41 (20.5)	6 (3.0)	90 (45)	90 (45)	20 (10)	96% patients received chemotherapy
Gynaecological cancer Inoperable												
1.	Xiao et al., 2015	Retrospective	Cervical cancer	China	238	mGPS (0/1/2)	107 (45.0)	29 (12.2)	138 (58.0)	71 (29.8)	29 (12.2)	Chemotherapy and radiotherapy
2.	Roncolato et al., 2018	Prospective	Endometrial cancer	Multinational	516	mGPS (0/1/2)	_	_	282 (54.7)	123 (23.8)	111 (21.5)	Chemotherapy and best supportive care
3.	Seebacher et al., 2019	Retrospective	Cervical cancer	Austria	116	GPS	_	_	41 (35.3)	56 (48.3)	19 (16.4)	Best supportive care for recurrent disease
Combined Total					1594				999 (62.7)	394 (24.7)	201 (12.6)	
Prostate cancer Operable												
1.					–				–	–	–	
Total												
Prostate cancer Inoperable												
1.	Linton et al., 2013	Prospective	Prostate cancer	Multinational	112	mGPS (2 vs. 0) (1 vs. 0)	>5: 36 (32.1)	27 (24.1)	76 (67.9)	17 (15.2)	19 (16.9)	Docetaxel and prednisone treatment
2.	Owari et al., 2018	Retrospective	Renal, prostate and urethral cancer	Japan	111	mGPS (0/1/2)	_	_	82 (74)	26 (23)	3 (3)	84% treated with radiotherapy
Combined Total					223				158 (70.9)	43 (19.3)	22 (9.9)	
Gastro-oesophageal Operable												

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
1.	Kobayashi et al., 2008	Retrospective	Oesophageal squamous cell carcinoma	Japan	48	GPS (0/ 1 and 2)	_	_	27 (56.3)	16 (33.3)	5 (10.4)	Neoadjuvant chemoradiotherapy (nCRT)
2.	Kobayashi et al., 2010b	Retrospective	Oesophageal squamous cell carcinoma	Japan	65	GPS (0 and 1)	_	_	43 (66.2)	16 (24.6)	6 (9.2)	60% patients received neoadjuvant chemoradiotherapy
3.	Dutta et al., 2011b	Retrospective	Oesophageal cancer	UK	112	GPS (0/1/2)	_	_	99 (88.4)	13 (11.6)	0 (0)	27.7% patients received neoadjuvant therapy and 12.5% received adjuvant therapy
4.	Dutta et al., 2011a	Retrospective	Gastro-oesophageal cancer	UK	121	GPS (0/1/2)	_	_	99 (81.8)	16 (13.2)	6 (5.0)	55.4% patients received neoadjuvant and 15.7% received adjuvant therapy
5.	Crumley et al., 2011	Retrospective	Gastro-oesophageal cancer	UK	100	GPS (0/1/2)	_	_	87 (87)	13 (13)	0 (0)	Adjuvant and neoadjuvant therapy
6.	Vashist et al., 2011	Retrospective	Oesophageal cancer	Germany	495	GPS (0/1/2)	_	_	268 (54.1)	166 (33.5)	61 (12.3)	No adjuvant or neoadjuvant therapy
7.	Dutta et al., 2012b	Retrospective	Oesophageal cancer	UK	98	GPS (0/1/2)	_	_	87 (88.8)	9 (9.2)	2 (2.0)	48.0% received neoadjuvant therapy and 18.4% received adjuvant therapy
8.	Feng et al., 2014	Retrospective	Oesophageal cancer	China	493	GPS (0/1/2)	_	_	316 (64.1)	121 (24.5)	56 (11.4)	Adjuvant chemotherapy and radiotherapy
9.	Nakamura et al., 2014	Retrospective	Oesophageal cancer	Japan	168	mGPS (0/1/2)	_	_	137 (81.6)	19 (11.3)	12 (7.1)	7.7% received neoadjuvant therapy while 36.9% received adjuvant therapy
10.	Matsuda et al., 2015	Retrospective	Oesophageal cancer	Japan	199	GPS (0/1/2)	10 (5.0)	12 (6.0)	108 (54.3)	68 (34.2)	23 (11.5)	49.8% patients received neoadjuvant chemotherapy and radiotherapy
11.	Arigami et al., 2015	Retrospective	Oesophageal cancer	Japan	238	mGPS (0/1/2)	_	_	168 (70.6)	54 (22.7)	16 (6.7)	Adjuvant therapy not specified
12.	Xu et al., 2015	Retrospective	Oesophageal squamous cell carcinoma	China	468	GPS/mGPS (0/ 1/2)	108 (23)	89 (19)	GPS: 336 (71.8) mGPS: 360 (76.9)	GPS: 101 (21.6) mGPS: 77 (16.5)	GPS: 31 (6.6) mGPS: 31 (6.6)	41.9% patient received adjuvant chemotherapy and radiotherapy
13.	Hirahara et al., 2015	Retrospective	Oesophageal cancer	Japan	141	GPS (0/1/2)	18 (12.8)	27 (19.1)	109 (77.3)	23 (16.3)	9 (6.4)	Adjuvant therapy not specified
14.	Walsh et al., 2016	Retrospective	Oesophageal cancer	Ireland	223	mGPS (0 vs. 1/ 2)	_	_	174 (78.0)	_	mGPS 1&2: 49 (22.0)	48.9% patients received neoadjuvant chemoradiotherapy, 29.6% patients received chemotherapy
15.	Otowa et al., 2016	Retrospective	Oesophageal cancer	Japan	100	Pre-NAC mGPS (0/1-2) Post-NAC mGPS (0/2) NAC = neoadjuvant chemotherapy	_	_	Pre: 82 (82.0) Post: 90 (90.0)	Pre: 7 (7.0) Post: 0 (0)	Pre: 11 (11.0) Post: 10 (10.0)	All patients received neoadjuvant chemotherapy

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
16.	Toyokawa et al., 2016	Retrospective	Thoracic Oesophageal Squamous Cell Carcinoma	Japan	185	GPS (0 vs 1/2)	_	_	171 (92.5)	13 (7.0)	1 (0.5)	24.9% patients received neoadjuvant therapy
17.	Nozoe et al., 2011	Prospective	Gastric cancer	Japan	232	GPS (0/1/2) mGPS (0/1/2)	58 (25.0)	62 (26.7)	140 (60.3)	64 (27.6)	28 (12.1)	Adjuvant therapy not specified
18.	Kubota et al., 2012	Retrospective	Gastric cancer	Japan	1017	GPS (0/1/2)	_	_	956 (94.0)	40 (3.9)	21 (2.1)	Adjuvant therapy not specified
19.	Dutta et al., 2012a	Retrospective	Gastric cancer	UK	120	GPS (0/1/2)	_	_	97 (80.8)	18 (15.0)	5 (4.2)	Patients received both adjuvant and neoadjuvant therapy
20.	Wang et al., 2012	Retrospective	Gastric cancer	China	324	GPS (0/1/2)	62 (19.1)	32 (9.9)	248 (76.5)	58 (17.9)	18 (5.6)	64.8% patients received adjuvant chemotherapy
21.	Jiang et al., 2012	Retrospective	Gastric cancer	Japan	1710	mGPS (0/1/2)	145 (8.5)	162 (9.5)	1565 (91.5)	78 (4.6)	67 (3.9)	Adjuvant therapy not specified
22.	Takeno et al., 2014	Retrospective	Gastric cancer	Japan	552	mGPS (0/1/2)	_	_	494 (89.5)	24 (4.3)	34 (6.2)	Adjuvant therapy not specified
23.	Hirashima et al., 2014	Retrospective	Gastric cancer	Japan	294	mGPS (0/1/2)	_	_	174 (59.2)	84 (28.6)	36 (12.2)	3.1% patients received neoadjuvant chemotherapy
24.	Aurello et al., 2014	Retrospective	Gastric cancer	Italy	102	mGPS (0/1/2)	53 (51.9)	55 (53.9)	49 (48.0)	25 (24.5)	28 (27.5)	66.7% patients received adjuvant chemotherapy
25.	Melling et al., 2016	Retrospective	Gastric cancer	Germany	88	GPS (0/1/2)	_	_	42 (47.7)	22 (25.0)	24 (27.3)	Neoadjuvant and adjuvant therapy not specified
Gastro-oesophageal cancer Inoperable												
1.	Crumley et al., 2006	Retrospective	Gastro-oesophageal cancer	UK	258	GPS (0/1/2)	_	_	92 (36)	121 (47)	45 (17)	Palliative chemotherapy and radiotherapy
2.	Crumley et al., 2008	Retrospective	Gastro-oesophageal cancer	UK	65	GPS (0/1/2)	_	_	26 (40)	31 (48)	8 (12)	Cisplatin based chemotherapy
3.	Zhang et al., 2014	Retrospective	Oesophageal cancer	China	212	mGPS (0,1,2)	122 (57.6)	134 (63.3)	90 (42.5)	78 (36.8)	44 (20.8)	Radiotherapy and cisplatin based chemo
4.	Elahi et al., 2004	Retrospective	Gastric and colorectal cancer	UK	Gastric: 66	GPS (0/1/2)	47 (71.2)	25 (37.9)	Gastric: 17 (25.8)	Gastric: 26 (39.4)	Gastric: 23 (34.8)	Palliative chemotherapy and supportive care
5.	Hwang et al., 2011	Retrospective	Gastric cancer	Korea	402	GPS: (1&2)	140 (34.9)	77 (19.2)	238 (59.2)	111 (27.6)	53 (13.2)	Cisplatin based chemotherapy
6.	Jeong et al., 2012	Retrospective	Gastric cancer	Korea	104	mGPS: (1 & 2)	_	_	58 (55.8)	29 (27.9)	17 (16.3)	Palliative chemotherapy
7.	Sachlova et al., 2014	Retrospective	Gastric cancer	Czech Rep	91 Total 64 (treated with chemo)	GPS (1&2)	_	_	37 (41)	31 (34)	23 (25)	Palliative platinum based chemotherapy
8.	Namikawa et al., 2016	Retrospective	Gastric cancer	Japan	244	GPS (0/1 or 2)	_	_	GPS:150 (61.5)	GPS: _	GPS: 1&2: 94 (38.5)	Combination chemotherapy including trastuzmab
						mGPS (0/1 or 2)	_	_	mGPS: 143 (58.6)	mGPS: _	mGPS 1&2: 101 (41.4)	
9.	Arigami et al., 2016	Retrospective	Gastric cancer	Japan	68	GPS: 1&2	_	_	35 (51.5)	27 (39.7)	6 (8.8)	Chemotherapy and chemoradiotherapy
10.	Hsieh et al., 2016	Retrospective	Gastric cancer	Taiwan	256	mGPS (> 1)	_	_	66 (26)	100 (39)	90 (35)	Combination Chemotherapy
11.	Okuno et al., 2017	Prospective	Oesophageal cancer	Japan	131	GPS (0/1/2)	_	_	56 (42.8)	48 (36.6)	27 (20.6)	Radiotherapy and standard cisplatin vs. Radiotherapy and low dose cisplatin

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
Combined Total					9590				6941 (72.4)	1670 (17.4)	979 (10.2)	
Haematological cancer Inoperable												
1.	Chou et al., 2015	Retrospective	Haematological cancer	China	217	GPS: (1&2)	181 (83.4)	156 (71.9)	15 (6.9)	56 (30.9)	146 (62.2)	Best supportive palliative care
2.	Jung et al., 2015	Retrospective	B-cell Lymphoma	Korea	213	L-GPS: 1&2	135 (63.4)	43 (20.2)	75 (35.2)	109 (51.2)	29 (13.6)	R-CHOP chemotherapy.
Combined Total					430				90 (20.9)	165 (38.4)	175 (40.7)	
Renal cancer Operable												
1.	Qayyum et al., 2012	Prospective	Renal cell cancer	UK	79	GPS (0/1/2)	_	_	57 (72.2)	19 (24.1)	3 (3.7)	Adjuvant therapies not specified
2.	Lamb et al., 2012	Retrospective	Renal cancer	UK	169	GPS (0/1/2)	_	_	117 (69.2)	46 (27.2)	6 (3.6)	Adjuvant therapies not specified
3.	Tsujino et al., 2017	Retrospective	Renal cancer	Japan	219	mGPS (0/1/2)	_	_	184 (84.0)	20 (9.1)	15 (6.9)	Adjuvant therapies not specified
4.	Fukuda et al., 2018	Retrospective	Renal cancer	Japan	170	GPS (0/1/2)	_	_	56 (33)	67 (39)	47 (28)	Chemotherapy and immunotherapy as part of cryoreductive treatment
5.	Inamoto et al., 2017	Retrospective	Urethreal cancer	Japan	574	GPS (0/1/2)	_	_	332 (57.8)	132 (23.0)	110 (19.2)	Adjuvant therapies not specified
6.	Son et al., 2018	Retrospective	Urethelial cancer	South Korea	1137	mGPS (0/1/2)	219 (19.3)	158 (13.8)	918 (80.7)	148 (13.0)	71 (6.2)	30.6% treated with adjuvant chemotherapy
7.	Owari et al., 2018	Retrospective	Renal and urethral cancer	Japan	69	GPS (0/1/2)	_	_	36 (52.2)	19 (27.5)	14 (20.3)	56.5% treated with radiotherapy
Renal cancer Inoperable												
1.	Ramsey et al., 2007	Retrospective	Renal cell cancer	UK	119	GPS: (0/1/2)	84 (71)	16 (14)	33 (28)	72 (60)	14 (12)	Active Immunotherapy
2.	Ramsey et al., 2008	Prospective	Renal cell cancer	UK	23	GPS (0/1/2)	_	_	8 (35)	6 (26)	9 (39)	Palliative immunotherapy
Combined Total					2559				1741 (68.0)	529 (20.7)	289 (11.3)	
Colorectal Cancer Operable												
1.	Ishizuka et al., 2007	Retrospective	Colorectal cancer	Japan	315	GPS (0/1/2)	76 (24.1)	100 (21.8)	183 (58.1)	89 (28.3)	43 (13.6)	Neoadjuvant treatments not specified
2.	McMillan et al., 2007	Retrospective	Colorectal cancer	UK	316	mGPS (0/1/2)	101 (32.0)	54 (17.1)	185 (58.5)	93 (29.5)	38 (12.0)	Adjuvant therapy not specified
3.	Leitch et al., 2007a	Retrospective	Colorectal cancer	UK	149	mGPS (0/1/2)	61 (40.9)	14 (9.4)	88 (59.1)	48 (32.2)	13 (8.7)	47.7% of patients received adjuvant therapy
4.	Roxburgh et al., 2009	Retrospective	Colorectal cancer	UK	287	mGPS (0/1/2)	_	_	171 (60)	82 (28)	34 (12)	Adjuvant therapy not specified
5.	Ishizuka et al., 2009a	Retrospective	Colorectal liver metastases	Japan	93	GPS (0/1/2)	_	_	63 (67.7)	24 (25.8)	6 (6.5)	Neoadjuvant therapy not specified
6.	Crozier et al., 2009	Prospective	Colon cancer	UK	188	mGPS (0/1/2)	_	_	79 (42.0)	80 (42.6)	29 (15.4)	28.7% patients received adjuvant therapy
7.	Roxburgh et al., 2010	Retrospective	Colon cancer	UK	287	mGPS (0/1/2)	_	_	143 (57)	102 (33)	42 (10)	Adjuvant chemotherapy
8.	Richards et al., 2010	Prospective	Colorectal cancer	UK	320	mGPS (0/1/2)	_	_	194 (61)	90 (28)	36 (11)	20.6% had adjuvant therapy
9.	Kobayashi et al., 2010a	Retrospective	Colorectal liver metastases	Japan	63	GPS (0/ 1 and 2)	_	_	57 (90.5)	4 (6.3)	2 (3.2)	84.1% patients received adjuvant chemotherapy

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
10.	Moug et al., 2011	Retrospective	Colorectal cancer	UK	206	GPS (0/1/2)	_	_	113 (54.9)	53 (25.7)	40 (19.4)	4.4% received neoadjuvant and 23.3% received adjuvant therapy
11.	Roxburgh et al., 2011b	Retrospective	Colorectal cancer	UK	302	GPS (0/1/2)	115 (38.1)	39 (12.9)	188 (62)	85 (28)	29 (10)	23.5% patients received adjuvant therapy
12.	Roxburgh et al., 2011a	Retrospective	Colon cancer	UK	76	mGPS (0/1 or 2)	42 (55.3)	31 (40.8)	34 (44.7)	33 (43.5)	9 (11.8)	100% patients received adjuvant chemotherapy
13.	Richards et al., 2012	Retrospective	Colorectal cancer	UK	343	GPS (0/1/2)	_	_	194 (56.6)	112 (32.7)	37 (10.7)	Adjuvant therapies not specified
14.	Sugimoto et al., 2012	Retrospective	Colorectal cancer	Japan	366	GPS (0/1/2)	_	_	mGPS 0/1: 335 (91.5)	_	31 (8.5)	Adjuvant chemotherapy
15.	Powell et al., 2012	Prospective	Colorectal cancer	UK	411	mGPS (0/1/2)	181 (44.0)	74 (18.0)	243 (59.1)	125 (30.4)	43 (10.5)	Adjuvant therapies not specified
16.	Ishizuka et al., 2012b	Retrospective	Colorectal cancer	Japan	271	GPS (0/1/2)	_	_	176 (64.9)	_	mGPS 1&2: 95 (35.1)	28.1% patients received adjuvant chemotherapy
17.	Guthrie et al., 2013a,b	Retrospective	Colorectal cancer	UK	206	mGPS (0/1/2)	_	_	132 (64)	33 (16)	41 (20)	28.2% patients received adjuvant chemotherapy
18.	Ishizuka et al., 2013b	Retrospective	Colorectal Stage IV cancer	Japan	108	GPS 2 vs. 0,1	45 (41.7)	55 (50.9)	37 (34.2)	42 (38.9)	29 (26.9)	Adjuvant chemotherapy
19.	Ishizuka et al., 2013a	Retrospective	Colorectal cancer	Japan	480	GPS (0/1/2)	_	_	270 (56.3)	150 (31.2)	60 (12.5)	Patients with stage IV received chemotherapy
20.	Son et al., 2013	Retrospective	Colon cancer	Korea	546	mGPS (2 vs. 0-1)	_	_	433 (80.0)	93 (17.0)	20 (3.0)	92.1% patients received chemotherapy
21.	Nozoe et al., 2014	Retrospective	Colorectal cancer	Japan	272	GPS (0/1/2)	_	_	179 (65.8)	62 (22.8)	31 (11.4)	Adjuvant therapies not specified
22.	Forrest et al., 2014	Retrospective	Colorectal cancer	UK	134	mGPS (0/1/2)	54 (40)	_	80 (60)	32 (24)	22 (16)	Adjuvant therapies not specified
23.	Sun et al., 2014	Retrospective	Colon cancer	China	255	mGPS (0/1/2)	_	_	163 (63.9)	71 (27.8)	21 (8.3)	Neoadjuvant or adjuvant not specified
24.	Nakagawa et al., 2014	Retrospective	Colorectal liver metastases	Japan	343	mGPS (0/1/2)	_	_	295 (86.0)	33 (9.6)	15 (4.4)	20.1% patients received neoadjuvant chemotherapy and 63.0% received adjuvant chemotherapy
25.	Shibutani et al., 2015	Retrospective	Colorectal cancer	Japan	254	GPS (0/1/2)	_	_	174 (68.5)	44 (17.3)	36 (14.2)	Adjuvant chemotherapy
26.	Ishizuka et al., 2016	Retrospective	Colorectal cancer	Japan	627	GPS (2/0, 1)	_	_	346 (55.3)	177 (28.2)	104 (16.5)	Adjuvant therapies not specified
27.	Park et al., 2016a	Retrospective	Colorectal cancer	UK	228	GPS (0/1/2)	_	_	131 (58)	71 (31)	26 (11)	57.5% received adjuvant therapy
28.	Park et al., 2016b	Retrospective	Colorectal cancer	UK	1000	mGPS (0/1/2)	370 (37.0)	260 (26.0)	635 (63.5)	207 (20.7)	158 (15.8)	24.8% received adjuvant therapy and 9.8% received neoadjuvant therapy
29.	Chan et al., 2016	Retrospective	Colorectal cancer	Australia	386	mGPS (0/1/2)	_	_	155 (40.2)	53 (13.7)	178 (46.1)	Patients with high-risk stage II and III colon cancer received adjuvant chemotherapy and those with stage II or III rectal cancers received neoadjuvant therapy

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
Colorectal Cancer Inoperable												
1.	Elahi et al., 2004	Retrospective	Gastric and colorectal cancer	UK	99	GPS (0/1/2)	71 (71.7)	26 (26.3)	28 (28.3)	45 (45.5)	26 (26.2)	Palliative chemotherapy and best supportive care
2.	Read et al., 2006	Prospective	Colorectal cancer	Australia	48	GPS (0/1/2)	48 (69)	14 (7)	15 (31)	26 (54)	7 (15)	Palliative chemotherapy and radiotherapy as well as supportive care
3.	Leitch et al., 2007b	Retrospective	Colorectal liver metastases	UK	84	GPS (0,1,2)	_	_	17 (20)	44 (52)	23 (28)	Palliative chemotherapy
4.	Ishizuka et al., 2009b	Retrospective	Colorectal cancer	Japan	112	mGPS: 1/2	40 (36)	79 (71)	72 (64)	4 (4)	36 (32)	FOLFIRI and FOLFOX chemotherapy
5.	Inoue et al., 2013	Retrospective	Colorectal cancer	Japan	245	mGPS (1-2 vs. 0)	_	_	133 (54.3)	78 (31.8)	34 (13.9)	FOLFOX and FOLFIRI chemotherapy
6.	Dreanic et al., 2015	Retrospective	Colorectal cancer	France	27	mGPS: 2 Inverse mGPS: 2	_	_	_	_	27 (100)	5-fluorouracil-based systemic chemotherapy and anti-VEGF
7.	Song et al., 2015	Retrospective	Colorectal cancer	Korea	177	mGPS: (0 vs. 1 or 2)	63 (35.6)	13 (7.3)	114 (64.4)	52 (29.4)	11 (6.2)	Best supportive care
8.	Thomsen et al., 2016	Prospective	Colorectal cancer	Norway and Denmark	374	mGPS (0/1/2)	_	_	165 (44.1)	166 (44.4)	43 (11.5)	Cetuximab and FLOX vs. Cetuximab and intermittent FLOX
Combined Total					9998				6020 (60.2)	2503 (25.0)	1475 (14.8)	
Head and Neck Operable												
1.	Farhan-Alanie et al., 2015	Retrospective	Oral SCC	UK	178	GPS (0/1/2)	_	_	131 (74)	25 (14)	22 (12)	70 patients had adjuvant therapy
Head andNeckInoperable												
1.	Li et al., 2017	Prospective	Nasopharyngeal cancer	China	249	GPS (0/1/2)	-	-	209 (83.9)	33 (13.3)	7 (2.8)	5.2% received radiotherapy and 94.8% received chemoradiotherapy
2.	Chang et al., 2017b	Retrospective	Head and neck cancer	Taiwan	143	GPS (0/1/2)	-	-	39 (27.3)	72 (50.3)	32 (22.4)	Concurrent chemoradiotherapy
3.	Chang et al., 2017a	Retrospective	Head and neck cancer	Taiwan	139	GPS (0/1/2)	-	-	32 (23.0)	72 (51.8)	35 (25.2)	All patients treated with concurrent chemoradiotherapy
Combined Total					709				411 (58.0)	202 (28.5)	96 (13.5)	
Hepato Pancreato Biliary Cancer Operable												
1.	Jamieson et al., 2011	Prospective	Pancreatic ductal cancer	UK	135	GPS (0/1/2)	_	_	74 (54.8)	31 (23.0)	30 (22.2)	54.8% patients received adjuvant therapy
2.	La Torre et al., 2012	Retrospective	Pancreatic cancer	Italy	101	GPS (0/1/2)	_	_	32 (31.7)	35 (34.7)	34 (33.6)	25.7% of patients received adjuvant chemotherapy and radiotherapy
3.	Jamieson et al., 2012	Retrospective	Pancreatic ductal adenocarcinoma	UK	173	mGPS (0/1/2)	_	_	95 (26.3)	37 (13.7)	41 (10.3)	38.7% patients received adjuvant chemotherapy
4.	Stotz et al., 2013	Retrospective	Pancreatic cancer	Austria	110	GPS (0/1/2)	_	_	73 (66.7)	21 (19)	16 (14.3)	80.0% received chemotherapy
5.	Wu et al., 2014	Retrospective	Gallbladder cancer	China	85	GPS (0 vs 1/2)	> 10: 43 (50.6)	< 35: 14 (16.5)	38 (44.7)		GPS 1&2: 47 (55.3)	15.3% patients received adjuvant chemotherapy

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
6.	Shiba et al., 2015	Retrospective	Gallbladder cancer	Japan	51	GPS (0/1/2)	_	_	38 (74.5)	8 (15.7)	5 (9.8)	Neoadjuvant and adjuvant therapy not specified
7.	Oshiro et al., 2013	Retrospective	Cholangiocarcinoma	Japan	62	GPS (0/1/2)	_	_	32 (50)	20 (34)	10 (16)	Neoadjuvant and adjuvant therapy not specified
8.	Shiba et al., 2013	Retrospective	Carcinoma of the ampulla of vater	Japan	30	GPS (0/1/2)	_	_	23 (76.7)	5 (16.7)	2 (6.6)	Neoadjuvant and adjuvant therapy not specified
9.	Ishizuka et al., 2011	Retrospective	HCC	Japan	300	hGPS (0, 1/2) *CRP > 0.3 mg/dl	>3: 63 (21.0)	150 (50.0)	237 (79.0)	22 (7.3)	41 (13.7)	Neoadjuvant and adjuvant therapy not specified
10.	Ishizuka et al., 2012a	Retrospective	HCC	Japan	398	GPS (0, 1/2)	263 (66.1)	238 (59.8)	156 (39.2)	214 (53.8)	28 (7.0)	Neoadjuvant and adjuvant therapy not specified
11.	Horino et al., 2013	Retrospective	HCC	Japan	352	GPS (0/1/2)	26 (7.4)	61 (17.3)	280 (79.5)	57 (16.2)	15 (4.3)	Neoadjuvant and adjuvant therapy not specified
12.	Huang et al., 2014	Prospective	HCC	China	349	GPS (0/1/2)	19 (5.4)	10 (2.9)	278 (79.7)	61 (17.4)	10 (2.9)	Neoadjuvant and adjuvant therapy not specified
13.	Ni et al., 2015	Retrospective	HCC	China	367	GPS (0/1/2)	_	_	GPS: 318 (86.6)	GPS: 45 (12.3)	GPS: 4 (1.1)	Neoadjuvant and adjuvant therapy not specified
14.	Okamura et al., 2015	Retrospective	HCC	Japan	256	mGPS (0/1/2)	_	_	mGPS: 331 (90.2)	mGPS: 32 (8.7)	mGPS: 4 (1.1)	
						GPS (0/1/2)			226 (88.3)	26 (10.2)	4 (1.5)	Neoadjuvant and adjuvant therapy not specified
15.	Abe et al., 2016	Retrospective	HCC	Japan	46	GPS (0/ 1,2)	3 (6.5)	32 (69.6)	14 (30.4)	_	mGPS 1&2: 32 (69.6)	Neoadjuvant and adjuvant therapy not specified
16.	Fu et al., 2016	Retrospective	HCC	China	Training: 772	GPS (0/1/2)	_	_	GPS 0: 672 (87.0)	GPS 1: 91 (11.8)	GPS 2: 9 (1.2)	Neoadjuvant and adjuvant therapy not specified
						mGPS (0/1/2)			mGPS 0: 696 (90.2)	mGPS 1: 68 (8.8)	mGPS 2: 8 (1.0)	
Hepato Pancreato Biliary Cancer Inoperable												
1.	Glen et al., 2006	Retrospective	Pancreatic cancer	UK	187	GPS (0/1/2)	120 (64)	62 (33)	56 (30)	80 (43)	51 (27)	Palliative treatment with platinum based chemotherapy
2.	Martin et al., 2014	Retrospective	Pancreatic cancer	Australia	124	mGPS: (0,1,2)	_	_	46 (37)	26 (21)	52 (42)	Chemotherapy for metastatic disease and radiotherapy for locally advanced disease
3.	Kasuga et al., 2015	Retrospective	Pancreatic cancer	Japan	61	mGPS: 2	17 (27.9)	22 (36.1)	mGPS 0/1: 49 (80.3)	_	mGPS: 2 12 (19.7)	Gemcitabine and S-1 combination therapy (FGS) as salvage chemotherapy
4.	Mitsunaga et al., 2016	Prospective	Pancreatic cancer	Japan	280 (Prospective: 141)	mGPS: 1 &2	>5: 46 (32.6)	_	79 (56.0)	39 (27.7)	23 (16.3)	GEM chemotherapy

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
	Moriwaki et al., 2014	Retrospective	Biliary tract cancer	Japan	Total: 62	Continuous: GPS (0 vs. 1/2)	_	_	19 (30.6)	17 (27.4)	26 (42.0)	Chemotherapy with GEM and CDDP regimens
5.	Zhou et al., 2015a	Prospective	HCC	China	224	GPS (0/1/2) mGPS (0/1/2)	40 (18)	24 (11)	GPS: 99 (44.2) mGPS: 115 (51.3)	GPS: 101 (45.1) mGPS: 85 (38.0)	GPS: 24 (10.7) mGPS: 24 (10.7)	TRACE chemotherapy
6.	Hurwitz et al., 2015	Prospective	Pancreatic cancer	USA	121	mGPS (0/1/2)	_	_	51 (42.2)	34 (28.1)	36 (29.7_	Capecitabine vs Capecitabine and ruxolitinib
Combined Total					4507				2985 (66.2)	970 (21.5)	552 (12.3)	
Pulmonary cancer operable												
1.	Pinato et al., 2014	Retrospective	Lung cancer	UK	Total:220 mGPS: 199	GPS (0/1/2)	66 (31)	65 (32)	131 (65.8)	39 (19.6)	29 (14.6)	Adjuvant radiotherapy and chemotherapy
2.	Miyazaki et al., 2015	Retrospective	NSCLC	Japan	94	GPS (0/1/2)	_	_	65 (67)	25 (25.8)	7 (7.2)	Neoadjuvant and adjuvant therapy not specified
3.	Kawashima et al., 2015	Retrospective	Lung cancer	Japan	1043	GPS (0/1/2)	98 (9.4)	87 (8.3)	897 (86)	107 (10)	39 (4)	Neoadjuvant and adjuvant therapy not specified
4.	Fan et al., 2016	Retrospective	Non-small cell lung cancer	China	1243	GPS (0/1/2) mGPS (0/1/2)	379 (30.5)	154 (12.4)	813 (65.4)	327 (26.3)	103 (8.3)	55.0% patients received chemotherapy and 17.7% patients received radiotherapy
Pulmonary cancer Inoperable												
1.	Forrest et al., 2003	Retrospective	NSCLC	UK	161	GPS (0/1/2)	132 (82)	22 (22)	27 (16.8)	101 (62.7)	33 (20.5)	Chemotherapy mainly cisplatin and radical radio
2.	Leung et al., 2012	Retrospective	Lung cancer	UK	261	mGPS (0/1/2)	149 (57)	41 (16)	59 (22.6)	163 (62.4)	39 (15.0)	Chemotherapy (mainly platinum based) and/or radical radiotherapy
3.	Gioulbasanis et al., 2012	Retrospective	Lung cancer	Greece	96	GPS (1&2)	_	_	68 (70.8)	18 (18.8)	10 (10.4)	Platinum-based chemotherapy
4.	Simmons et al., 2015	Prospective	Lung cancer	Greece	390	mGPS (0/1/2)	287 (73.6)	_	103 (26.4)	183 (46.9)	104 (26.7)	Best supportive care
5.	Zhou et al., 2015b	Retrospective	Lung cancer	China	359	mGPS 1&2	21 (33.7)	20 (5.6)	238 (66.3)	110 (30.6)	11 (3.1)	Radiotherapy and chemotherapy (Irinotecan, Etoposide)
6.	Jiang et al., 2015	Prospective	Lung cancer	China	138	GPS: 1&2	_	_	95 (68.8)	32 (23.2)	11 (8.0)	Cisplatin based chemotherapy
7.	Rinehart et al., 2013	Prospective	Lung cancer	USA	51	GPS (0/1/2)	_	_	9	32	10	Carboplatin and gemcitabine with or without dexamethasone
Combined Total					4035				2502 (62.0)	1137 (28.2)	396 (9.8)	
Multiple Cancers Operable												
Multiple Cancers Inoperable												
1.	Chua et al., 2012	Prospective	Multiple	Australia	68	mGPS (1&2)	43 (63.2)	17 (25.0	21 (31)	34 (50)	13 (19)	Single unit docetaxel treatment

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Table 1 (continued)

No: GPS/mGPS	Study	Type of Study	Cancer	Country	Patients (n)	Measure of SIR	CRP > 10 mg/l	Albumin < 35 g/l	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2	Additional Treatment
2.	Partridge et al., 2012	Retrospective	Multiple cancers	UK	102 (GPS 0/1/2)	mGPS (1&2)	-	-	16 (15.7)	20 (19.6)	66 (64.7)	Palliative best supportive care
3.	Laird et al., 2013	Prospective	Multiple cancers	UK	Total: 2456 1825 (Test) 631 (Validation)	mGPS: 1&2	Test: > 10: 1548 (63.0) Validation: > 10: 345 (54.7)	Test: < 35: 1281 (52.2) Validation: < 35: 463 (73.4)	Total: 563 Test: 277 (15.2) Validation: 286 (45.3)	Total: 712 Test: 544 (29.8) Validation: 168 (26.6)	Total: 1181 Test: 1004 (55.0) Validation: 177 (28.1)	Chemotherapy, radiotherapy and best supportive care
4.	Anshushaug et al., 2015	Retrospective	Multiple cancers	Norway	Total: 723 With mGPS:	GPS (1 & 2)	> 10: 312 (59.9)		209 (40.1)	131 (25.1)	181 (34.8)	Palliative radiotherapy and chemotherapy
5.	Miura et al., 2015	Prospective	Multiple cancers	Japan	521160	GPS 1&2	-	-	86 (7.4)	251 (21.6)	823 (70.9)	Palliative best supportive care
6.	de Paula et al., 2016	Prospective	Multiple cancers	USA	459	mGPS 1&2	> 10: 93 (20.3)	-	366 (79.7)	31 (6.8)	62 (13.5)	Palliative chemopotherapy and best supportive care
7.	Tan et al., 2015	Prospective	Multiple cancers	Australia	Total: 114 mGPS: 101	mGPS: 1/2	> 10: 51 (50.5)	-	50 (49.5)	-	mGPS 1&2: 51 (50.5)	Chemotherapy
Combined Total					4867				1311 (26.9)	1179 (24.2)	2377 (48.8)	

operable colorectal cancer. These studies included both retrospective (n = 26) and prospective studies (n = 3). These included studies carried out in the UK (n = 15), Japan (n = 11), China (n = 1), Korea (n = 1) and Australia (n = 1). In total 3,356 (38%) of patients were system-atically inflamed (Tables 1 and 2).

Eight studies including 1,166 patients were identified in inoperable colorectal cancer. These studies included both retrospective (n = 6) and prospective studies (n = 2). These included studies carried out in the UK (n = 2), Japan (n = 2), France (n = 1), Korea (n = 1), Australia (n = 1) and Norway/Denmark (n = 1). In total 622 (53%) of patients were systematically inflamed (Tables 1 and 3).

4.10. Studies of the systemic inflammatory response in patients with head and neck cancer

A single study was identified in patients with operable head and neck cancer. This contained 178 patients, was retrospective, carried out in the UK and showed that 47 (26%) of patients were systemically in-flamed (Tables 1 and 2). Three studies including 531 patients were identified in inoperable head and neck cancer. These studies included both retrospective (n = 1) and prospective studies (n = 1). These in-cluded studies carried out in Taiwan (n = 2) and China (n = 1). In total 251 (47%) of patients were systematically inflamed (Tables 1 and 3).

4.11. Studies of the GPS/ mGPS in patients with Hepato Pancreato Biliary Cancer

Sixteen studies including 3,587 patients were identified in operable hepato pancreato biliary cancer. These studies included both retro-spective (n = 14) and prospective studies (n = 2). These included studies carried out in Japan (n = 8), the UK (n = 2), China (n = 4), Italy (n = 1), and Austria (n = 1). In total 1,001 (28%) of patients were systematically inflamed (Tables 1 and 2).

Seven studies including 920 patients were identified in inoperable hepato pancreato biliary cancer. These studies included both retro-spective (n = 5) and prospective studies (n = 2). These included stu-dies carried out in Japan (n = 3), UK (n = 1), USA (n = 1), China (n = 1) and Australia (n = 1). In total 333 (36%) of patients were system-atically inflamed (Tables 1 and 3).

4.12. Studies of the GPS/ mGPS in patients with Pulmonary Cancer

Four studies including 2,579 patients were identified in operable pulmonary cancer. All of these studies were retrospective. These in-cluded studies carried out in the Japan (n = 2), UK (n = 1) and China (n = 1). In total 1,001 (27.9) of patients were systematically inflamed (Tables 1 and 2).

Seven studies including 1,456 patients were identified in inoperable pulmonary cancer. These studies included were both retrospective (n = 4) and prospective studies (n = 3). These included studies carried out in the UK (n = 2), China (n = 2), Greece (n = 2) and the USA (n = 1). In total 857 (59%) of patients were systematically inflamed (Tables 1 and 3).

4.13. Studies of the GPS/mGPS in patients with Multiple Cancer Types

No articles were identified in patients with operable multiple types of cancer. Seven studies including 4,867 patients were identified in inoperable multiple cancer types. These studies included both retro-spective (n = 3) and prospective studies (n = 4). These included stu-dies carried out in the UK (n = 2), Australia (n = 2), USA (n = 1), Japan (n = 1) and Norway (n = 1). In total 3,556 (73%) of patients were systematically inflamed (Tables 1 and 3).

Table 2
Summary of studies using GPS/mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

	Patients (n)	GPS/mGPS 0	GPS/mGPS 1	GPS/mGPS 2
Breast cancer	181	100 (55.2)	61 (33.7)	20 (11.1)
Bladder cancer	2200	1443 (65.6)	613 (27.9)	144 (6.5)
Gynaecological cancer	1594	999 (62.7)	394 (24.7)	201 (12.6)
Prostate cancer	223	158 (70.9)	43 (19.3)	22 (9.9)
Gastro-oesophageal cancer	9590	6941 (72.4)	1670 (17.4)	979 (10.2)
Haematological cancer	430	90 (20.9)	165 (38.4)	175 (40.7)
Renal cancer	2559	1741 (68.0)	529 (20.7)	289 (11.3)
Colorectal cancer	9998	6020 (60.2)	2503 (25.0)	1475 (14.8)
Head and Neck cancer	709	411 (58.0)	202 (28.5)	96 (13.5)
Hepato Pancreato Biliary cancer	4507	2985 (66.2)	970 (21.5)	552 (12.3)
Pulmonary cancer	4035	2502 (62.0)	1137 (28.2)	396 (9.8)
Multiple cancer	4867	1311 (26.9)	1179 (24.2)	2377 (48.8)

Table 3
Summary of studies using mGPS to stratify patients undergoing operative and non-operative treatment for cancer.

	Patients (n)	GPS/ mGPS 0	GPS/ mGPS 1	GPS/mGPS 2
Breast Cancer				
Operative	_	_	_	_
Non-operative	181	100 (55.2)	61 (33.7)	20 (11.1)
Bladder cancer				
Operative	2133	1410 (66.1)	596 (27.9)	127 (6.0)
Non-operative	67	33 (49.3)	17 (25.4)	17 (25.4)
Gynaecological cancer				
Operative	724	538 (74.3)	144 (19.9)	42 (5.8)
Non-operative	870	461 (53.0)	250 (28.7)	159 (18.3)
Prostate cancer				
Operative	_	_	_	_
Non-operative	223	158 (70.8)	43 (19.3)	22 (9.9)
Gastro-oesophageal cancer				
Operative	7693	6076 (79.0)	1068 (13.9)	549 (7.1)
Non-operative	1897	865 (45.6)	602 (31.7)	430 (22.7)
Haematological cancer				
Operative	_	_	_	_
Non-operative	430	90 (20.9)	165 (38.4)	175 (40.7)
Renal cancer				
Operative	2417	1700 (70.3)	451 (18.7)	266 (11.0)
Non-operative	142	41 (28.9)	78 (54.9)	23 (16.2)
Colorectal cancer				
Operative	8832	5476 (62.0)	2088 (23.6)	1268 (14.4)
Non-operative	1166	544 (46.7)	415 (35.6)	207 (17.7)
Head and Neck cancer				
Operative	178	131 (74)	25 (14)	22 (12)
Non-operative	531	280 (52.7)	177 (33.3)	74 (14.0)
Hepato Pancreato Biliary cancer				
Operative	3587	2586 (72.1)	673 (18.8)	328 (9.1)
Non-operative	920	399 (43.4)	297 (32.3)	224 (24.3)
Pulmonary cancer				
Operative	2579	1903 (73.8)	498 (19.3)	178 (6.9)
Non-operative	1456	599 (41.1)	639 (43.9)	218 (15.0)
Multiple cancers				
Operative	_	_	_	_
Non-operative	4867	1311 (26.9)	1179 (24.2)	2377 (48.8)
Total Operative	28,143			
Total Non-operative	12,750			
Combined Total	40,893			

4.14. Combined Inoperable and Operable Studies

Inoperable and operable cancer studies are summarised in Tables 2 and 3. The percentage of patients with operable cancer (n > 28,000) who were systemically inflamed varied from 21% to 38% (gastro-esophageal and colorectal cancer respectively Table 3). The most commonly studied cancer was colorectal cancer (n > 8,500 patients) and 38% were systemically inflamed (Table 3). The percentage of pa-tients with inoperable cancer (n > 12,000) who were systemically in-flamed varied from 29% to 79% (prostate and haematological cancers, Table 3). Furthermore, a commonly studied cancer was colorectal cancer (n > 1,100 patients) and 53% were systemically inflamed (Table 3). Overall, the percentage of patients (n > 40,000) who were systemically inflamed varied from 28% to 63% according to tumour type (gastroesophageal and multiple cancers respectively). The most commonly studied cancer was colorectal cancer (n~10,000 patients) and 40% were systemically inflamed overall (Table 2).

5. Discussion

In the present narrative review of the prevalence of the systemic inflammatory response (as evidenced by GPS/mGPS) in more than 40,000 patients with cancer it was clear that the elevation of the GPS/ mGPS was common and the prevalence was greater in advanced cancer compared with operable cancer. In particular, of the patients with op-erable cancer, no specific tumour type had more than 50% of patients with an elevated systemic inflammatory response as measured by the GPS/mGPS. In contrast, of the patients with inoperable cancers, gastro-oesophageal cancer, colorectal cancer, hepato pancreato biliary cancer, pulmonary cancer and multiple cancers all had more than 50% of pa-tients with an elevated systemic inflammatory response as measured by the GPS/mGPS. Therefore, it is clear that the presence of a systemic inflammatory response is a common prognostic feature of established cancer, especially advanced cancer.

The results of the present review are consistent with the report of Proctor and colleagues who first studied the prevalence of the mGPS before and after diagnosis in an unselected cohort of patients with cancer and reported that “the proportions of mGPS 1 and 2 were greater following a diagnosis of cancer (Proctor et al., 2010).” Taken together these results would indicate that the systemic inflammatory response is present at the earliest stages of cancer and increases as the cancer progresses. Given the independent prognostic value of the mGPS this may suggest that the systemic inflammatory response reflects or pro-motes tumour progression. Irrespective, these results have implications for the future stratification and treatment of both operable and in-operable disease in patients with cancer.

The implications for patient stratification are clear and there is now evidence of the GPS/mGPS being used in the randomised clinical trial setting (Dolan et al., 2018a). However, the importance of the systemic inflammatory response in the development of cachexia (Cederholm et al., 2017, Cederholm et al., 2019) and in particular the loss of lean tissue (Abbass et al., 2019) is of considerable importance since it highlights those patients likely to develop cachexia between tumour type (breast cancer/ lung cancer) and tumour stage (operable/

inoperable). The implications for treatment to mitigate the effects of the systemic inflammatory response are less clear in patients with breast cancer and operable cancer. In contrast, in lung cancer and in advanced inoperable cancer there are clear implications for the use of the sys-temic inflammatory response as a therapeutic target (Diakos et al., 2014).

In summary, the systemic inflammatory response, as evidenced by the GPS/mGPS, was common in both primary operable and advanced inoperable cancers particularly in patients with cancers of the lungs and gastrointestinal tract. Therefore, the systemic inflammation "iceberg" is in plain sight and should be factored into future treatment plans of patients with cancer.

Ethical approval and consent to participate

This is a narrative review as a result ethical approval is not needed.

Consent to publish

All authors have granted their consent to publish.

Data availability

All data relating to this study is contained within the tables.

Funding

This research is funded by the University of Glasgow.

Conflicts of interest

There are no conflict of interests to report.

Acknowledgements

No acknowledgements to report.

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